



Blood & Immunity

The blood

It is the fluid that circulates inside the cardiovascular system.

Colour: the arterial blood is bright red, while the venous blood is dark or bluish red.

Specific gravity (S.G): the S.G for blood cells = 1090, and for plasma = 1030, and for the whole blood = 1060.

[**Note:** the specific gravity for water = 1000].

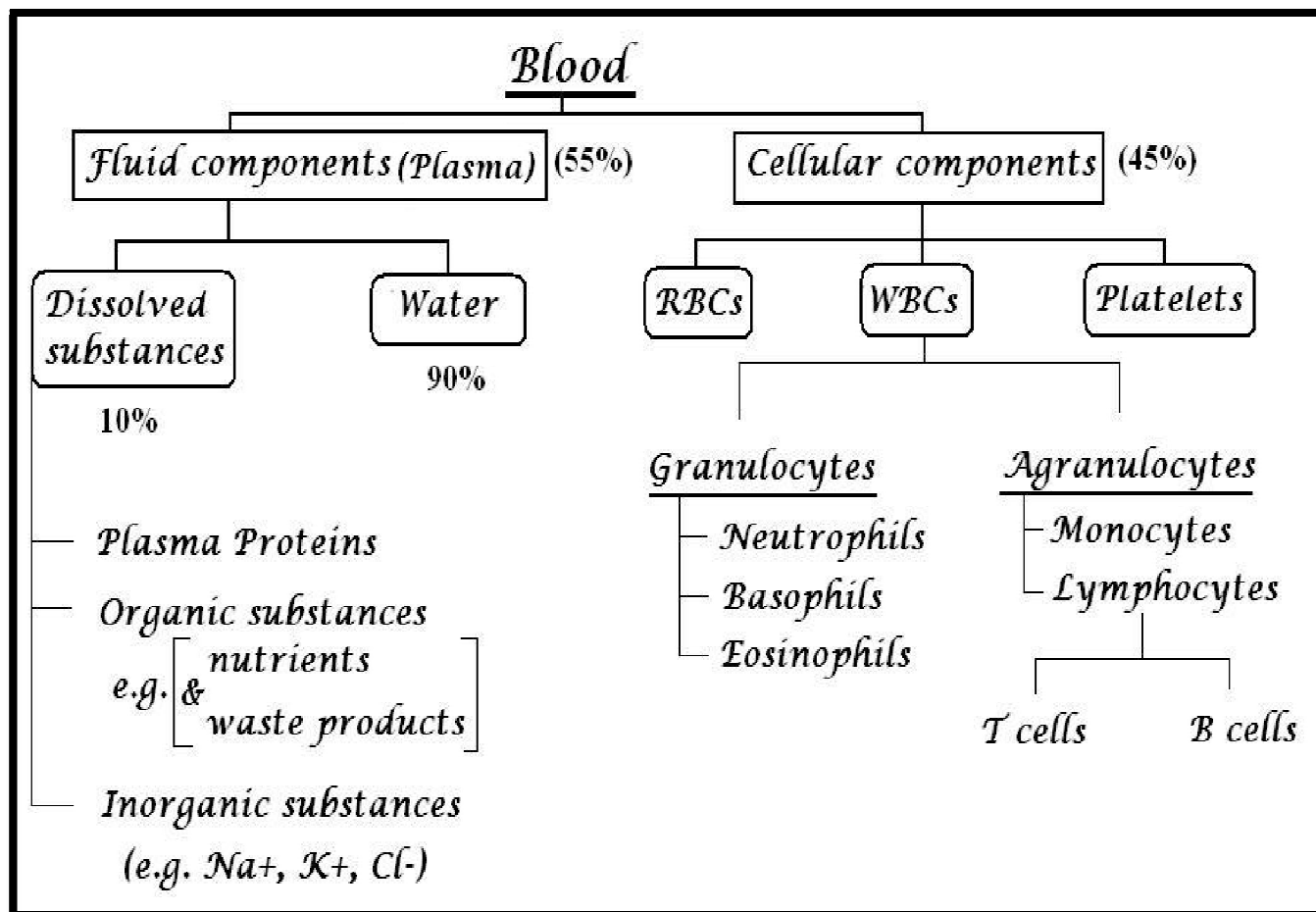
Viscosity: the viscosity of water = 1, and of plasma = 2, and of whole blood = 4. It is mainly due to blood cells and plasma proteins.

Osmotic pressure (OP): the OP of the water is about **300 m.osm. /L** [about 5000 mmHg Or (7 atmosphere)] [each 1 m.osm. /L = 19.3 mmHg].

It is mainly due to crystalloids (e.g. NaCl). The colloids (plasma proteins) OP is only 25 – 30 mmHg (mainly due to albumin).

General functions of the blood:

- 1- Transport of gases (O_2 & CO_2) and transport of nutrients, hormones, active substances and waste products.
- 2- Defend the body from the invading pathogens by means of white blood cells [which attack by themselves and by the production of antibodies].
- 3- Has components that prevent blood loss when blood vessels injured [by platelets & clotting factors].
- 4- It helps in the maintenance of homeostasis.



Packed cell volume (Hematocrit):

It is the percentage ratio of RBCs volume to the whole blood (it is about 45 %).

Plasma proteins (Pl.Pr):

The plasma of the blood contains about 6 – 8 gm of proteins / 100 mg of plasma.

Protein	Concentration	M.W
Albumin	3.5 – 5 gm%	70,000
Globulin (α , β , & γ)	2 – 3.5 gm%	150,000
Fibrinogen	400 mg%	400,000
prothrombin	10 mg%	350,000

Functions of Pl.Pr

1- Albumin is responsible for about 80% of the osmotic pressure of plasma. This is because it has the highest concentration and the smallest molecular size (great number of molecules) between the other proteins.

Note: the crystalloids (e.g. Na⁺, K⁺, Cl⁻) has no role in the creation of plasma osmotic pressure, because their concentrations are equal between the intravascular and interstitial fluid compartments; so the osmotic effect is zero.

2- The antibodies (gamma globulins) protect the body from the invading pathogens [e.g. bacteria, virus, toxin, etc].

3- The fibrinogen is the main Pl.Pr responsible for plasma viscosity (because of its large molecular weight).

4- The fibrinogen and prothrombin are clotting factors used during clot formation.

5- The **Pl.Pr** act as protein reserve that is used during starvation.

6- The **Pl.Pr** act as carriers for many substances like [vitamins / hormones (e.g. thyroxin, insulin) / metals (e.g. iron, copper) / ions (e.g. Ca⁺)]. The binding of these substances with **Pl.Pr** acts as reservoir for these substances, and prevent their filtration through the kidneys and their loss in the urine.

Albumin / Globulin (A / G) ratio

It is the ratio of albumin to globulins in plasma. It is normally 1/1 to 1/8. This ratio decreases when the albumin decrease as in cases of [malnutrition, malabsorption, loss of albumin in kidney diseases or in sever burns].

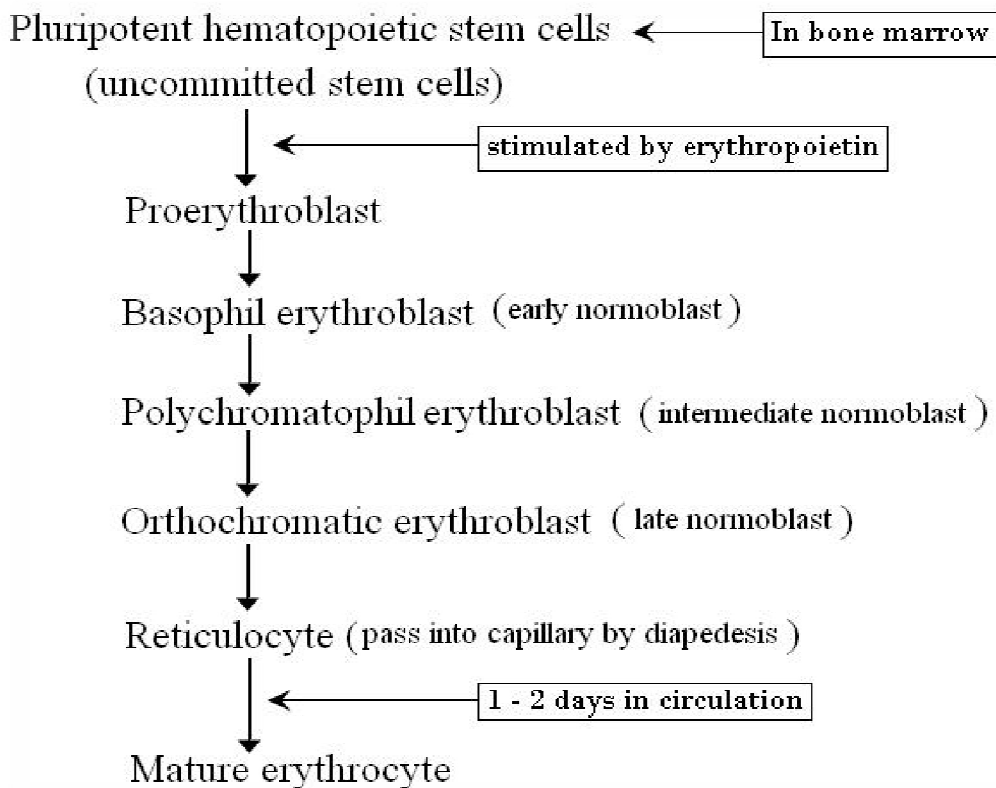
Red blood corpuscles (RBCs) (Erythrocytes)

Number: 5 millions/mm³ in adult male, 4.5 millions/mm³ in adult female, and more in newly born infants.

Shape: circular, biconcave, non nucleated disc. This shape increases the surface area of the RBC, and enables it to pass through the narrow capillary without rupturing.

Dimensions (size): 90 cubic micron (μ^3) in volume, 7.5 micron in diameter, and 2 microns in thickness.

Origin (site of formation): in fetus, the RBCs are formed in the liver and spleen. In children, they are formed in bone marrow of all bones, but in adults (> 20 y) the RBCs are formed in the bone marrow of the flat (membranous) bones (e.g. sternum, ribs, skull, and vertebrae). This bone marrow called red (active) bone marrow.

(Erythropoiesis)

The whole process of erythropoiesis takes about 5 days.

Life span: the RBCs live for about 120 days $\pm$ 7 days.

The **reticulocytes** form about 1% of RBCs in normal blood [because of its short life span (about 1 – 2 days)].

Factors affecting erythropoiesis

The synthesis (genesis) of RBCs is affected by many factors which include:

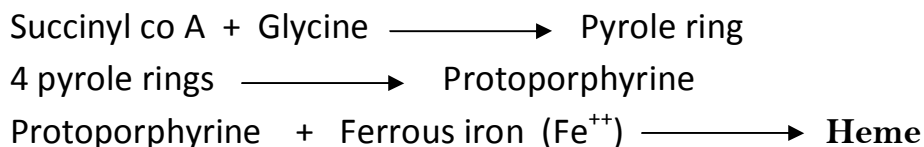
- 1- The hypoxia ($\downarrow$ O₂ supply to a tissue) is the main (primary) stimulus for erythropoiesis. The hypoxia stimulates the secretion of erythropoietin hormone from the kidneys (mainly; about 90%) and from the liver (10%). The erythropoietin stimulates all stages of erythropoiesis (but mainly the conversion of hemopoietic stem cells to proerythroblast).
- 2- **Hormones:** androgens (e.g. testosterone), thyroid hormones (T3 & T4), and glucocorticoids (e.g. cortisone), all of them stimulate the erythropoiesis.
- 3- **Metals:** the iron in ferrous state (Fe ++) is needed for formation of heme part of hemoglobin. The copper and cobalt also aid in the formation of RBCs.

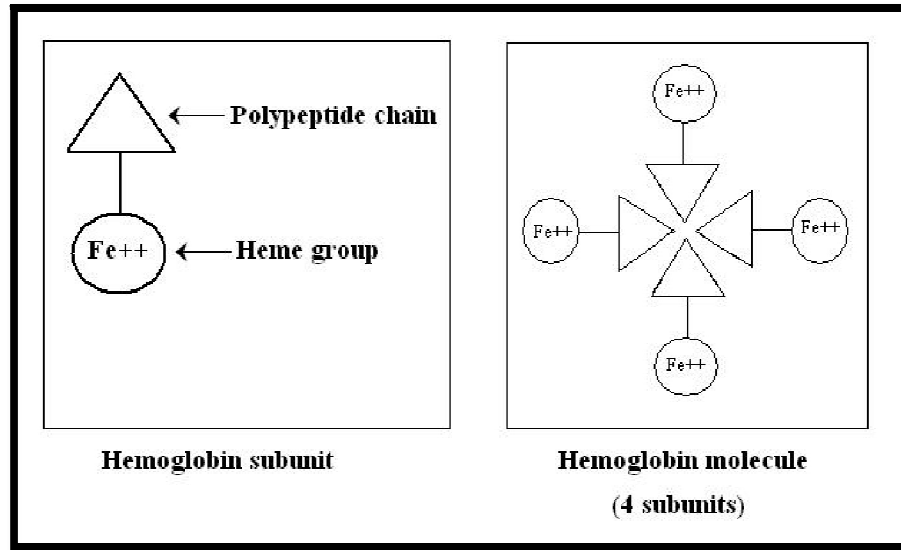
Hemoglobin (Hb)

The **Hb** is a complex inside the RBC that is responsible for the transport of gases in the blood. Its value is about 15 gram/100 ml of blood in adults [16 in males, 14 in females]. Each hemoglobin molecule is composed of 4 subunits. Each unit is composed of:

- a- Heme group: it is composed of iron protoporphyrine.
- b- Polypeptide chain of amino acids.

The heme is synthesized by the following mean:





Types of Hb

The Hb type depends on the composition of amino acids in the polypeptide chains.

A- Normal (physiological) types:

- 1- Adult Hb (**Hb-A**): it forms 98% of the normal adult hemoglobin. It contains 2 α chains and 2 β chains.
- 2- **Hb-A₂**: it forms 2% of normal adult Hb. It contains 2 α chains and 2 δ chains.
- 3- Fetal Hb (**Hb-F**): it is present before birth, and is replaced soon after birth (within about 6 months) by Hb-A. It contains 2 δ chains and 2 γ chains.

B- Abnormal (pathological) types (hemoglobinopathies):

- 1- **Hb-S**: this type contains 2 abnormal β chains, but with normal α chains. This will lead to precipitation of Hb → RBC sickle in shape → sickle cell anemia.
Note: the newly borne is free from the manifestations of this problem which appears after the age of about 6 months (because **Hb-F** does not contain β chains).
- 2- **Hb-H**: The α chains are absent. Instead, the person has 4 β chains [this is called α thalassemia]. In β thalassemia, the β chains are absent, but there are 4 α chains.

Reactions (forms) of Hb:

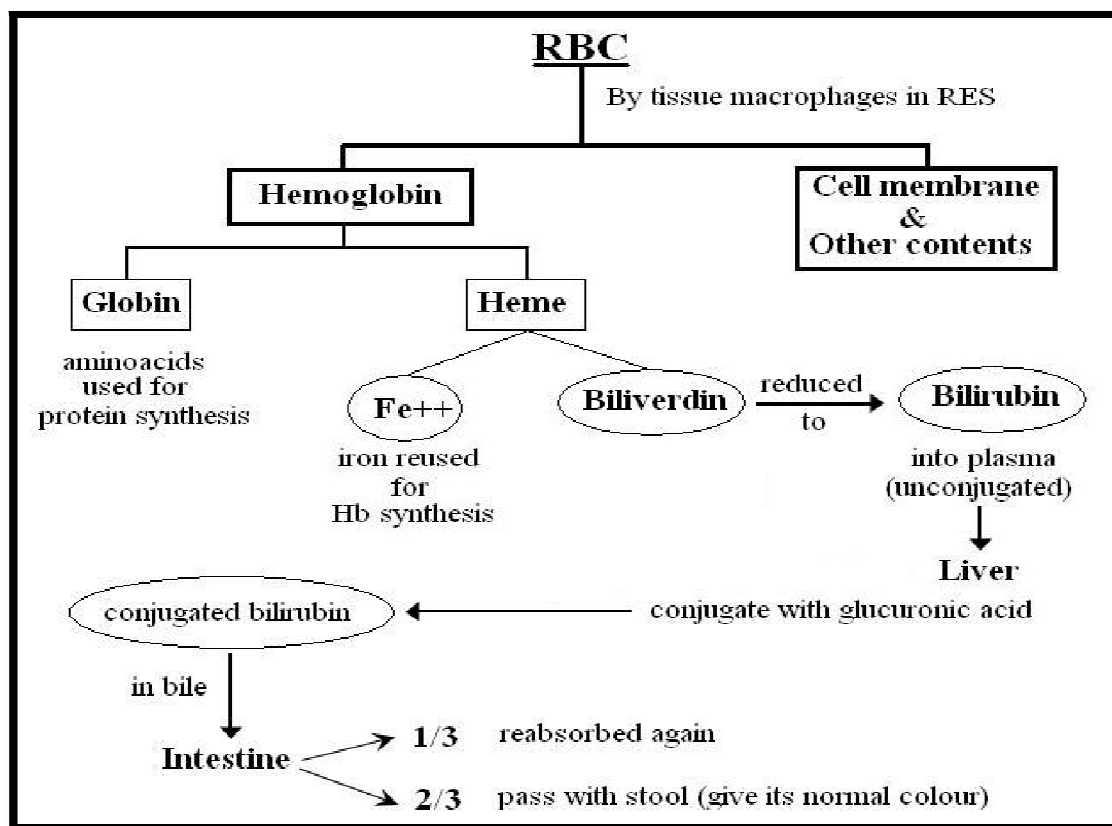
The form of Hb depends on the reaction of the heme part of Hb.

A- Normal forms:

- 1- Oxyhemoglobin: $\text{Hb} + \text{O}_2$. Each subunit of Hb is attached by its ferrous iron (Fe^{++}) with one molecule of oxygen [i.e. each Hb molecule bind with 4 O_2 molecules].
- 2- Carb aminohemoglobin: $\text{Hb} + \text{CO}_2$. The CO_2 is attached to the protein part of Hb.

B- Abnormal forms:

- 1- Carboxyhemoglobin: $\text{Hb} + \text{CO}$ (carbon monoxide). The CO attach to the Fe^{++} . The affinity of Hb to CO is 210 times $> \text{O}_2$.
- 2- Methemoglobin: it is the hemoglobin that has ferric (Fe^{+++}) instead of ferrous when the blood expose to an oxidizing agent. The (Fe^{+++}) is unable to carry O_2 . In normal persons this is prevented by the enzyme NADH methemoglobin reductase, and the congenital absence of this enzyme will lead to the emergence of hereditary methemoglobinemia.



Iron metabolism

The total quantity of iron in the body is about 4 grams. 65% of it is in the form of **Hb**, and 30% is stored iron in the form of ferritin.

Absorption: the ingested Fe^{+++} in the food is reduced in the stomach by reducing agents [e.g. HCl & vitamin C]. The Fe^{++} then bind with a protein called apotransferrin which transfer it across the epithelial cells as transferrin.

Transport: when the Fe^{++} reaches the blood, it binds again with apotransferrin to form transferrin that transports the iron to its storage or utilization sites.

Storage: the iron is stored mainly in the liver where it combines with apoferritin to form ferritin, which is released into plasma on demands. But if the amount of iron exceeds the storage capacity → precipitation of insoluble iron (*hemosiderin*) → damage of storing cells (a disease called *hemosiderosis*).

Vitamin B12 (cyanocobalamin)

The stored amount of vitamin **B₁₂** in the liver equals the body needs for 5 years.

Metabolism: to be absorbed, the vitamin **B₁₂** should combine with [intrinsic factor (**IF**)] which is secreted from the parietal cells of gastric mucosa. The vit **B₁₂ – IF** complex then is absorbed at the terminal ileum. In the blood, the vitamin B12 is transported by transcobalamin to be used by tissues, or stored mainly in the liver.

Anemia

Definition: decrease the RBCs count or Hb content or both below the normal range for age and sex.

Types of anemia:

The anemia is classified according to the size of RBCs and to the Hb content in each RBC into:

I] Normocytic Normochromic anemia: the RBCs size is normal (Normocytic) and the Hb content in each RBC is normal (Normochromic).

Causes:

1- Hemolysis of RBCs (hemolytic anemia): it may be due:

a- Intravascular (IV) causes:

- i- Cell membrane defect [e.g. hereditary spherocytosis].
- ii- Hb defect [e.g. sickle cell anemia, thalassemia (α & β)].
- iii- Enzymatic defect [Glucose 6 phosphate dehydrogenase deficiency (favism)].

b- Extravascular (EV) causes:

- i- Drugs.
- ii- Snake venoms.
- iii- Bacterial toxins.

2- Acute blood loss (Hemorrhagic anemia).

3- Bone marrow depression (Aplastic anemia): it may occur in:

- i- Excessive exposure to radiation (e.g. X-ray).
- ii- Some viral infections.
- iii- Some drugs (e.g chemotherapy).
- iv- Invasion of bone marrow by malignant cells.

II] Microcytic Hypochromic anemia: the RBCs size is below the normal (Microcytic) and the Hb content in each RBC is decreased (Hypochromic).

it is due to deficiency of iron, so it is called (iron deficiency anemia).

Causes:

1- ↓ iron intake: as in malnutrition or starvation.

2- ↓ absorption: it may be due to:

- a-** ↓ reducing agents [e.g. HCl & vitamin C].
- b-** Presence of phytic acid (in tea), phosphate or oxalate in food.
- c-** ↓ bile (because it contains *apotransferrin* that is necessary for absorption).

3- Chronic blood loss: this is could be because of:

- a- GIT bleeding (e.g. peptic ulcer or piles).
- b- Hematuria.
- c- Excessive menstruation (most common cause of anemia in females).

4- ↓ storage [as in liver diseases].

5- ↑ requirements [as in pregnancy, lactation, and rapid growth in puberty].

III] Macrocytic hyperchromic anemia (megaloblastic anemia): the RBCs size is above the normal (macrocytic) and the Hb content in each RBC is increased (hyperchromic). It is due to deficiency of vitamin B12 or folic acid.

Causes:

1- ↓ intake.

2- ↓ absorption: it could be due to:

- a- ↓ **IF** due to atrophy of gastric mucosa (called pernicious anemia).
- b- Disease or excision of the terminal ileum (absorption site).
- 3- ↓ storage [as in liver diseases].

Clinical manifestations of anemia

[Pallor – Palpitation – Fatigue – Fainting – Headache – Blurring of vision].

Diagnosis of anemia

The anemia is diagnosed by decrease in the measurements of all of the following:

- 1- RBCs count.
- 2- Hb content.
- 3- Hematocrit value (packed cell volume).

To know the type of anemia, we have to calculate the following hematological indices:

1- Mean corpuscular volume (MCV):

$$MCV = \frac{\text{Hematocrite} \times 10}{\text{RBCs count} \backslash \text{mm}^3 \text{ . in millions}} \quad \text{Normally} = \frac{45 \times 10}{5} = 90 \pm 7 \mu^3.$$

2- Mean corpuscular hemoglobin (MCH):

$$MCH = \frac{\text{Hb content} \times 10}{\text{RBCs count} \backslash \text{mm}^3 \text{ . in millions}} \quad \text{Normally} = \frac{15 \times 10}{5} = 30 \pm 3 \text{ Pg.}$$

3- Mean corpuscular hemoglobin concentration (MCHC):

it is the amount of Hb in 100 ml packed RBCs.

$$MCHC = \frac{\text{Hb content} \times 100}{\text{Hematocrit}} \quad \text{Normally} = \frac{15 \times 100}{45} = 33 \pm 3\% .$$

All of these indices are:

- 1- Normal in normocytic normochromic anemia.
- 2- ↓ in microcytic hypochromic (iron deficiency) anemia.
- 3- ↑ in macrocytic hyperchromic (megaloblastic) anemia.

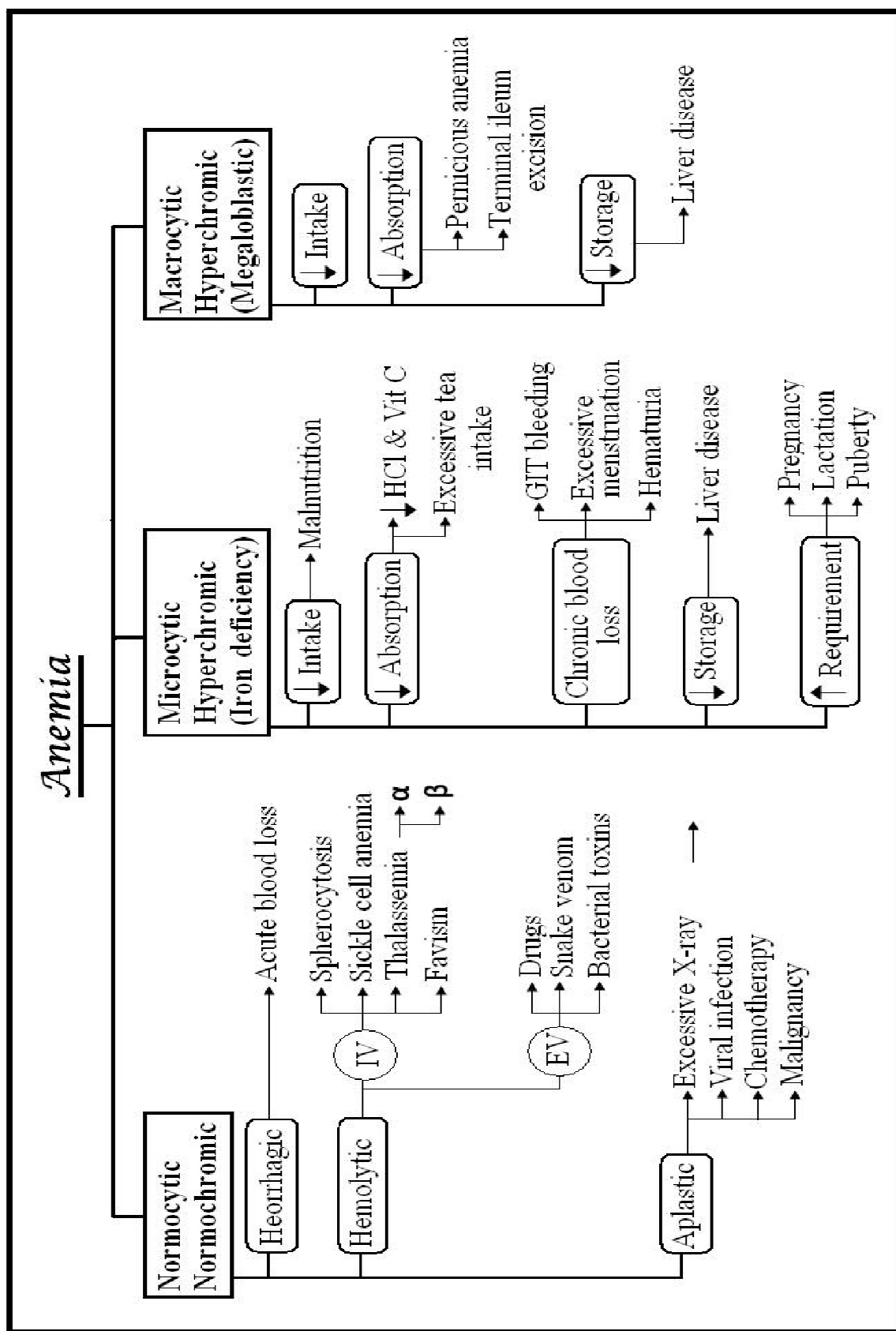
Polycythemia

Definition: abnormal ↑ in RBCs count.

Types:

- 1- Primary polycythemia (polycythemia vera): it is due to a tumor like condition of blood forming cells.
- 2- Secondary polycythemia: it may be physiological (as in high altitude) or pathological.

The polycythemia ↑ blood viscosity → ↑ blood pressure and ↓ blood flow to tissues.



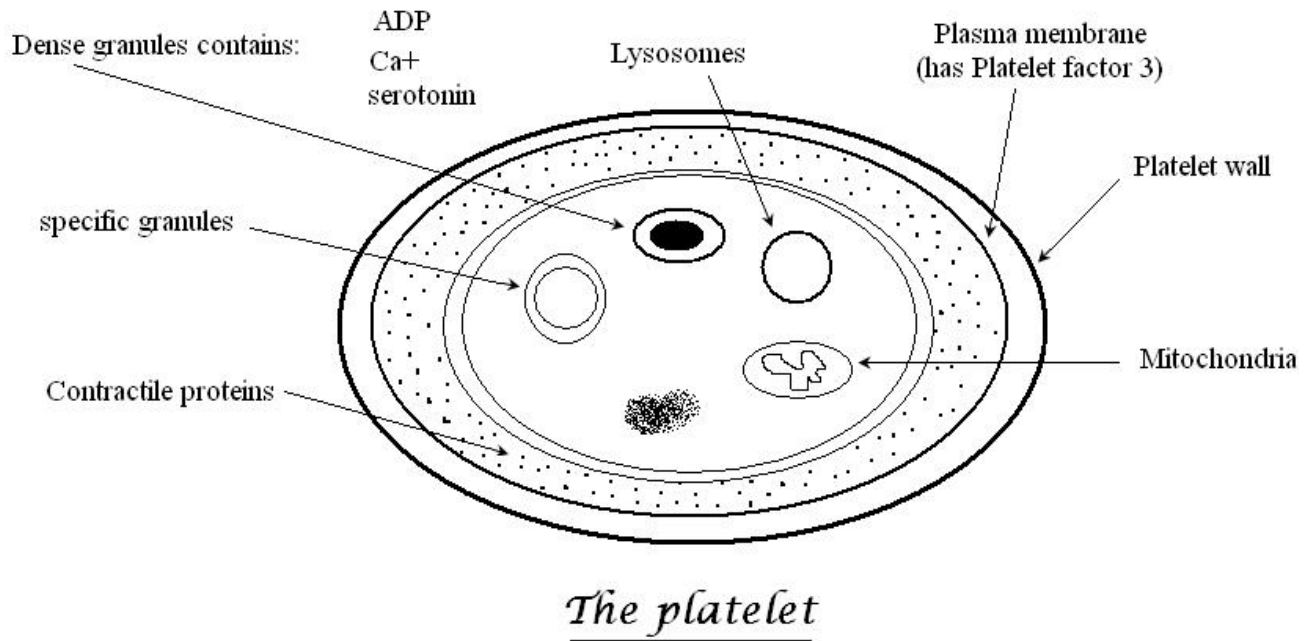
Platelets

Number (count): 150,000 – 350,000 / mm³ (250,000 in average).

Shape: Non-nucleated rounded discs 2 – 4 μ.

Formation: formed in bone marrow from megakaryocytes. It lives for about 10 days.

Structure:



Function: The platelets are important for hemostasis.

Hemostasis

Definition: it is the stoppage of bleeding from an injured blood vessel. It is done by 3 mechanisms in the following order:

1- Local vasoconstriction: the area of injury in the affected blood vessel undergoes vasoconstriction to slow the escape of blood from it (thromboxan A₂, serotonin and ADP that are secreted by the platelets have a role in this mechanism). The local vasoconstriction is enough to stop bleeding from very small vessels.

2- Formation of platelet plug: the platelets form the platelet plug (which is enough to stop the bleeding from small blood vessels) as the following:

a- Platelet adhesion: the injured endothelium attracts the von willibrand factor which is present in the plasma. This factor in turn will attract and adhere to the circulating platelets.

b- After their adhesion, the platelets release its contents (e.g. ADP, thromboxane A₂, etc) which will activate more platelets to aggregate and adhere to the formed plug until the injured vessel becomes closed.

3- Formation of blood (fibrin) clot: the blood clot is needed to close the large injuries. It is formed of meshwork of fibrin threads entrapping blood cells and platelets. After aggregation of platelets, they secrete platelet factor 3 which will activate some clotting factors that will form the fibrin clot.

Clotting factors

I	Fibrinogen	VIII	Antihemophilic A factor
II	Prothrombin	IX	Antihemophilic B factor
III	Tissue thromboplastin (tissue factor)	X	Stuart power factor
IV	Calcium	XI	Antihemophilic C factor
V	Labile factor	XII	Contact factor (Hageman factor)
VII	Stable factor	XIII	Fibrin stabilizing factor

Notes:

1- There is no factor **VI**.

2- Platelet factor 3, prekallikrein, and high molecular weight (HMW) kininogen are considered as clotting factors.

3- The prostacycline released by vascular endothelium prevents the platelet aggregation on the intact endothelia surface.

The clot is formed by these factors through 2 pathways:

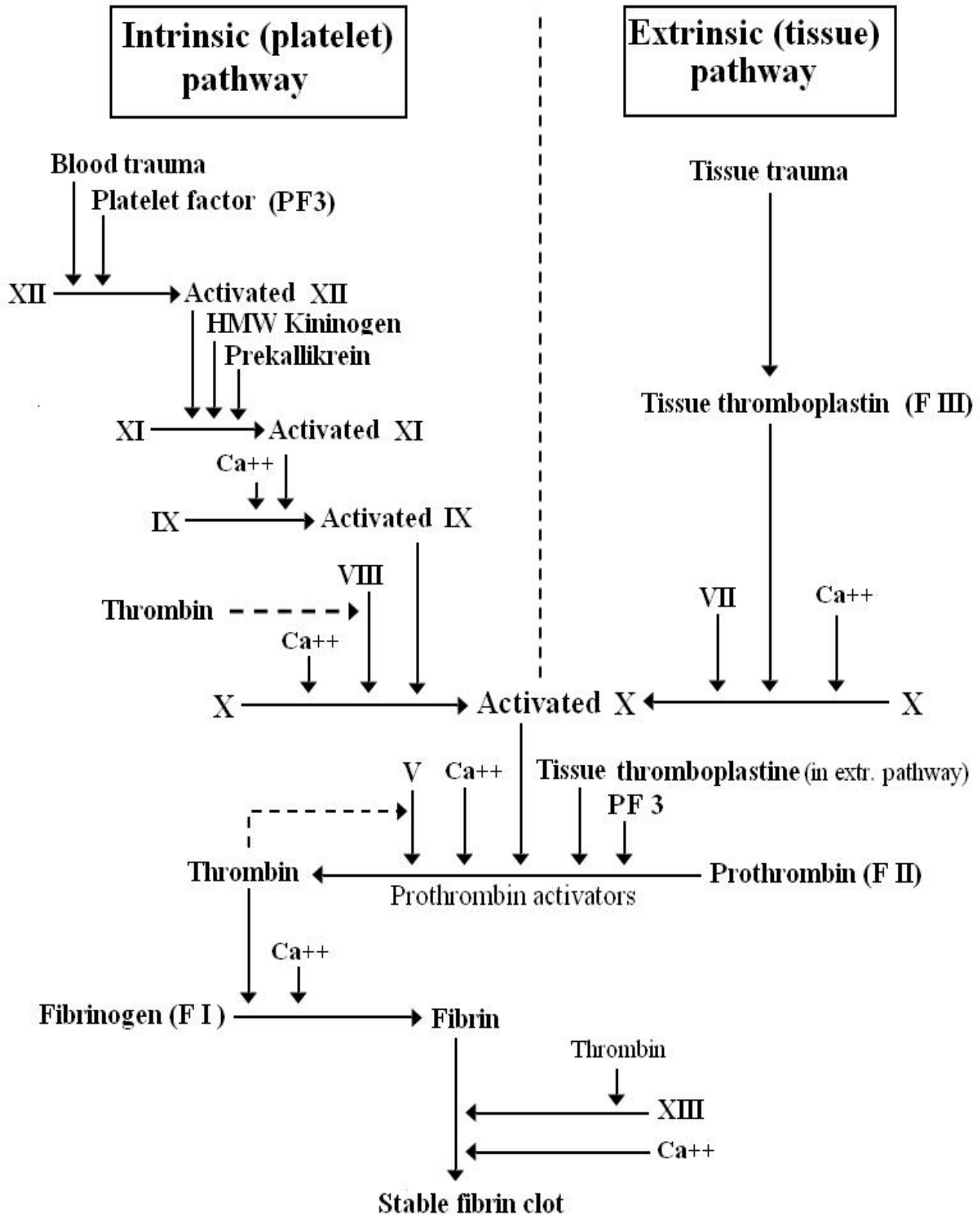
1- Intrinsic pathway: all factors needed are present in the blood.

2- Extrinsic pathway: needs tissue factor (tissue thromboplastin) which is not present in plasma (released only from injured tissue).

- Both of these pathways are complementary in the formation of colt.
- The Ca^{+} (in the ionized state) is required for promotion of all reactions in the intrinsic and extrinsic pathways (except the 2 steps in intrinsic pathway).

	Intrinsic pathway	Extrinsic pathway
Factors needed	All are present in the blood.	Some are not present in blood (e.g. tissue thromboplastine).
Site of occurrence	Inside & outside the body (e.g. in test tube).	Only inside the body.
Duration	Slow (4 – 8 min) to form clot.	Rapid (only 20 sec) to form clot.
Clot formed	Large & firm.	Small and weak.
Main function	Formation of the definitive clot.	Rapid formation of thrombin which helps the intrinsic pathway.

Note: serum = plasma – some clotting factors (mainly fibrinogen).
So, the serum is [defibrinated plasma].



Classification of clotting factors

The clotting factors are classified according to their common characters into:

1- Fibrinogen group: it includes [fibrinogen (factor I), factors (V, VIII, and XIII)].

They are characterized by:

- a-** All of them are activated by thrombin.
- b-** They are completely utilized by clot, i.e. they are not present in serum after formation blood clot.

2- Prothrombin group: it includes: [prothrombin (factor II), factors (VII, IX, X)].

They are characterized by:

- a-** They need vitamin K for their synthesis in the liver.
- b-** Present in the serum (except prothrombin).

3- Contact group: it includes: [factors XI & XII]. They are characterized by:

- a-** Stimulated by contact with rough surface.
- b-** Present in serum.

Natural anti clotting mechanisms

There are certain protective mechanisms that prevent clotting of the blood inside the blood vessels. These mechanisms include:

A- Mechanisms related to endothelium:

- 1-** Smoothness of the endothelium.
- 2-** Secretion of prostacycline (prostaglandin I₂) by the platelets which inhibits the aggregation of platelets.

B- Mechanisms related to blood:

- 1- Continuous blood flow.
- 2- Presence of heparin (anticoagulant) which is secreted from mast cells and basophils.
- 3- Presence of antithrombin III (secreted by the liver).
- 4- Presence of protein C and protein S (natural anticoagulants).

c- Fibrinolysis:

Definition: breakdown of the already formed blood clot.

It is done by the action of plasmin enzyme (fibrinolysin) which is present in its inactive form (plasminogen). This plasmin breaks (degrades) the fibrin and fibrinogen into Fibrinogen degradation products (FDP).

This mechanism is important for reopening of blood vessels after their closure by clot.

Tests for Hemostasis

- 1- Platelet count:** it is ↓ in thrombocytopenia purpura.
 - 2- Bleeding time:** It is the stoppage of bleeding from injured skin without formation of blood clot. It is a test for platelet function (i.e. plug formation). Normally = 1 – 5 minutes. It is prolonged in [purpura / von willibrand's disease].
 - 3- Clotting time:** it is the time needed by the blood to form a clot in vitro (outside the body). It is a non specific test for intrinsic pathway. Normally = 5 – 10 minutes.
 - 4- Prothrombin time (P.T):** it is a test for extrinsic pathway. Normally = 10 – 14 seconds. It is prolonged in [vitamin K deficiency / patient taking caumarins (anticoagulant tablets)].
 - 5- Activated partial thromboplastin time (APTT):** it is a test for intrinsic pathway [it is a test for contact factors (factors XI, XII)]. Normally = 30 – 40 seconds. It is prolonged in [Hemophilia / patient taking Heparin].
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Disorders of Hemostasis

1- Intravascular clotting (thrombosis):

it is a state of continuous formation of blood clots inside the blood vessels.

Causes:

- a- Venous stasis [as in prolonged recumbancy (e.g. bed ridden)].
- b- Roughness of endothelium [e.g. atherosclerosis].
- c- Hyperviscosity [e.g. polycythemia / thrombocytosis].

This problem may lead to formation of:

- i- **Thrombus**: clot fixed to a blood vessel wall.
- ii- **Embolus**: clot moving freely in the circulation.

Both of thrombus and embolus will ↓ the blood supply to the supplied area → ischemia.

2- Purpura: it is a small punctuate hemorrhages under the skin. It is due to:

- a- Thrombocytopenia (↓ platelet count to less than 50,000).
- b- Thrombasthenia (abnormal function of platelets).

3- Hemophilia: it is a disease characterized by bleeding tendency. It is a disease of males (sex linked recessive). There are 3 types of hemophilia:

- a- Hemophilia A (classic hemophilia) (85%): it is due to factor **VIII** deficiency.
- b- Hemophilia B (Christmas hemophilia) (10%): it is due to factor **IX** deficiency.
- c- Hemophilia C (5%): it is due to factor **XI** deficiency.

4- Vitamin K deficiency: this problem will lead to ↓ of prothrombin group of cl. Factors. [Prothrombin, **VII**, **IX**, **X**]. It is decreased in [newborns, prolonged use of antibiotics, liver diseases, etc].

5- Von willibrand's disease: it is a disease caused by deficiency of van willibrand factor.

Note: the diseases [2, 3, 4, and 5] are called Hemorrhagic diseases.

	Purpura	Hemophilia	Vit. K deficiency	Von willibrand's disease
Deficient factors	Platelets	VII or IX or XI	II, VII, IX, X	V W F
Bleeding time	Prolonged	Normal	Normal	Prolonged
clotting time	Normal	Prolonged	Prolonged	Prolonged
Prothrombin time	Normal	Normal	Prolonged	Normal
APTT	Normal	Prolonged	Nearly normal	Prolonged

White blood cells (WBCs) (leukocytes)

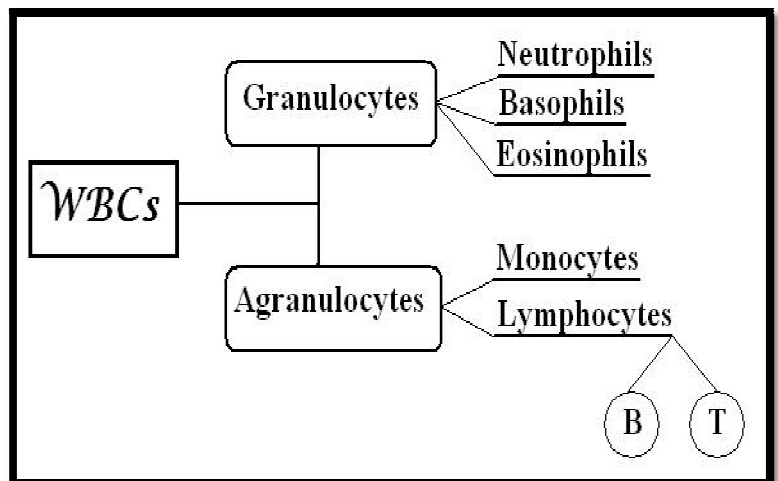
Total count: 4000 – 11,000 cells / mm³.

سكيم صغير لأنواع الكريات البيضاء

Site of formation: in bone marrow (Granulocytes & Monocytes) and lymphatic tissues (Lymphocytes).

Life span: it is variable:

- a- Granulocytes: 5 hours in blood, and 5 days in tissues.
- b- Monocytes: 10 hours in blood, months (or even years) in tissues.
- c- Lymphocytes: few hours in blood, months or years in tissues.



Types

I] Granulocytes: they contain granules in their cytoplasm. They include:

1- Neutrophils (microphages): they constitute about 60% of the total WBCs count. They are potent phagocytes that attack and destroy the invading bacteria. Each neutrophil can phagocytose 5 – 20 bacteria before it dies.

it perform its function by [Margination – Diapedesis (squeezing) – Amoeboid movement – Chemotaxis (attraction of Neutrophils by bacterial toxins) – Phagocytosis – Exocytosis].

2- Eosinophils: they constitute about 3% of total WBCs count.

They defend the body against parasites. They also slow and modulates the allergic reactions by detoxifying the inflammation induced substances (e.g. histamine) and destroying the antigen-antibody complex.

3- Basophils: they constitute about 1% of total WBCs count.

When they migrate to the connective tissue, they become (**mast cells**). The mast cells synthesize the heparin, and have a role in the generation of allergic reactions [produces inflammatory mediators, e.g. (histamine, bradykinin, serotonin)].

II] A granulocytes: they do not contain granules in their cytoplasm. They include:

1- Lymphocytes: (30% of the total WBCs count). They include B & T lymphocytes.

2- Monocytes: (6% of the total WBCs count). In the blood, they have no phagocytic activity. But when entering the tissues, they convert to highly phagocytic cells called (Macrophages). They can engulf large particles (e.g. whole RBC) and can engulf about 100 bacteria before it dies. So, they are more powerful phagocytic than Neutrophils.

Reticuloendothelial system (RES)

It is the group of tissues that contain fixed macrophages inside them. These macrophages are named according to the tissue [e.g. kuppfer cells (in liver) / alveolar macrophages (in lungs) / Histeocytes (in skin) / Osteoclasts (in bones) / Microglia (in brain) / Mesengial cells (in kidneys)]. This reticuloendothelial system has other functions that include:

- a- Removal of old RBCs, WBCs, and platelets.
- b- Formation of bilirubin from Hb released from old RBCs.
- c- Storage of iron.

Leukocytic count variation

- 1- Leukocytosis: it is $\uparrow$ of the total number of WBCs ($> 11,000$). It could be
 - a- Physiological: all the leukocytes types increase in the same proportion [e.g. in exercise, emotions, pregnancy].
 - b- Pathological: there is an increase in one type more than the other.
 - i- Neutrophilia: $\uparrow$ in pyogenic infections [abscess] or tissue damage [e.g. surgery].
 - ii- Eosinophilia: $\uparrow$ in parasitic infestation [e.g. bilharziasis], or in allergic conditions [bronchial asthma].
 - iii- Basophilia: $\uparrow$ in allergic conditions.
 - iv- Lymphocytosis: $\uparrow$ in viral infections [e.g. mumps], chronic bacterial infections [e.g. Tuberculosis (TB)].
- 2- Leucopenia: it is $\downarrow$ number of WBCs (< 4000).
- 3- Leukemia: it is a marked $\downarrow$ in WBCs due to malignant disease of bone marrow.
- 4- Agranulocytosis: it is marked $\downarrow$ in WBCs due to failure of bone marrow to produce WBCs due to [e.g. irradiation, drug intoxication].

Immunity

Definition: the ability of the body to resist foreign organisms or toxins that tends to damage the tissues and organs.

The immunity is of 2 types:

A- Non specific (innate) (inherent) immunity:

This type does not depend on the nature of the invading substance [i.e. not specific for certain substance (e.g. specific bacteria or certain foreign substance). It is inherited and exists with the human since birth. It includes:

[Skin / acidity of the stomach / phagocytic cells (mainly Neutrophils and macrophages) / Natural killer cells (special type of lymphocytes) / substances in the blood (e.g. interferon, complement system) / etc].

B- Specific (acquired) immunity:

It is the immunity that develops against specific antigens (bacteria, virus, toxins, etc) after weeks or months from their invasion to the body.

Antigen: large MW substance that can initiate immune response on its invasion to body.

Hapten: small MW subs. that can initiate immune response only after binding to one of the tissue proteins.

The acquired immunity is the function of Lymphocytes. The lymphocytes are classified functionally (not morphologically) into 2 types:

1- B Lymphocytes: they attack the invading pathogen (antigen) indirectly by formation of antibodies specific for this pathogen. So, it is responsible for humoral acquired immunity.

2- T Lymphocytes: they attack the invading antigen directly. Thus, it is responsible for cell mediated immunity.

I- Humoral (antibody mediated) immunity

It is the immunity mediated by circulating antibodies (Ab) that is produced by B Lymphocytes. It is performed in the following way:

- 1- When an antigen enters the body, the tissue macrophages phagocytose and present it to the B lymphocytes, this will activate these lymphocytes.
- 2- When the B lymphocytes become activated, they take the lymphoblasts appearance. Some of these lymphoblasts differentiate and proliferate into Plasma cells.
- 3- The plasma cells secrete large amount of antibodies into the circulation which is specific for the presented antigen that caused their formation (and Ab will attack the Ag). This process continues for several days or months until the plasma cells die.
- 4- Some of the lymphoblasts do not differentiate into plasma cells. Instead, they form a new B lymphocytes (similar to the original clone) called memory cells. These cells make the immunity to the subsequent exposures to the same antigen more rapid and more potent (secondary immune response).

Antibodies

They are gamma globulins produced by plasma cells in lymphoid tissue. They are also called immunoglobulins (Ig). There are 5 types of immunoglobulins [M,A,G,E,D].

- 1- IgM: it has the highest MW, so it can not cross the placenta. The ABO antibodies are of this type.
- 2- IgA: it is secreted from the circulation to the mucous membranes (e.g. lung, intestine) to produce local immunity. For this reason, it is called secretory Ig.
- 3- IgG: it has the smallest MW, so it can cross the placenta to reach the fetal circulation, so it is responsible for passive immunity transmitted from the mother to her fetus. The Rh antibodies & most of the antibacterial and antiviral Ab's are of this type.

4- IgD: it is found only in small amounts in serum. It may act as antigen receptors on the surface of lymphocytes.

5- IgE: rarely found as free Ab in the circulation. But it is found on the surface of basophils and mast cells which will stimulate their secretions of histamine & other inflammatory substances during allergic reactions.

Mechanism of action of antibodies

- 1- Agglutination: clumping of antigens to be destroyed by macrophages (agglutinins).
 - 2- Precipitation: precipitate the Ag-Ab complex (insoluble) in the blood (precipitins).
 - 3- Neutralization: the Ab covers the toxic site on the Ag (antitoxins).
 - 4- Lysis: Ab attack the cell membrane of cellular Ag → cell rupture (lysins).
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II- Cellular (cell mediated) immunity

It is the immunity mediated by the circulating T Lymphocytes.

Mechanism:

- 1- The tissue macrophages find and present the invading antigen to the T Lymphocytes (as occurs with B cell in humoral immunity). This will activate the T Lymphocytes.
- 2- When get activated, the T cells take the appearance of lymphoblasts. Some of these lymphoblasts differentiate into effector (activated) T cells which will enter the circulation and attack the invading antigen. The effector T cells are of 3 types:

A- Cytotoxic (killer) T cells: these cells directly attack the [bacteria, viruses, cancer cells and transplanted cells]. They kill them by release of cytotoxic substances directly to them.

B- Suppressor T cells: they prevent excessive immune response by inhibiting the function of B and other T Lymphocytes.

C- Helper T cells: they are the most abundant (75% of Lymphocytes). Their functions include:

- i- Stimulate the conversion of B cells into plasma cells.
- ii- Stimulate the production of antibodies by plasma cells.
- iii- Activate the macrophages and all types of T cells (cytotoxic, suppressor, and even the other helper T cells).

3- Formation of memory cells: as in B Lymphocytes.

Primary and secondary immune response

Primary immune response: it is the immune response that occurs on the 1st exposure to an antigen. It is [slow / weak / of short duration].

Secondary immune response: it is the immune response that occurs on the subsequent exposures of the body to the same antigen. It is [rapid / more potent / last longer].

Immunization

It is the potentiation of the immunity of the person either by:

- 1- Passive immunization: injecting the person with already prepared antibodies.
 - 2- Active immunization: stimulation of the acquired immunity by injecting the person with weak or dead organisms or modulated toxins (antigens).
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Immunological abnormalities

- 1- Immune deficiency: ↓ immunity due to either ¹congenital failure of development of immune system or ²acquired as in acquired immune deficiency syndrome (AIDS).

- 2- Hypersensitivity: ↑ immunity to one or more antigen [e.g. asthma, urticaria].
- 3- Autoimmunity: it is the formation of antibodies against the body's own protein.

Spleen

The spleen is part of the lymphoid tissue. Its functions include:

- 1- Stores about $\frac{1}{2}$ L of blood to deliver it on demand [e.g. in hemorrhage, exercise].
- 2- Formation of RBCs (in fetal life) and lymphocytes.
- 3- Destruction of old RBCs, WBCs, and platelets.
- 4- Contains lymphocytes & tissue macrophages that are mediated in immune response.

Blood groups

The blood groups are classified according to the antigens (agglutinogens) present on the RBCs membrane. The plasma usually contains antibodies (agglutinins).

There are many systems for grouping of blood; the most important are 2 systems:

- **ABO system**: in this system, there are 2 antigens (A & B) and 2 antibodies (A & B). By this system, the blood is divided into 4 blood groups:

Blood group	A	B	AB	O
% of population	40 %	10 %	5 %	45 %
Ag (on RBCs)	A	B	A & B	–
Ab (in plasma)	Anti B	Anti A	–	Anti A Anti B

• **Rh system**: this system constitutes the antigen D. The blood groups of this system are:

Blood group	Rh + ve	Rh - ve
% of population	85 %	15 %
Ag (on RBCs)	D	–
AB (in plasma)	–	Normally not present

Normally, the Rh-ve peoples have no anti D antibody, but they develop it on injection of **D** antigen [e.g. on blood transfusion, labor].

The anti **D** Ab is IgG (can cross the placenta) while the anti **A** & anti **B** are IgM (can't cross the placenta).

Erythroblastosis fetalis (Hemolytic disease of newborn)

Def: it is a disease of fetus or newborn characterized by agglutination & Hemolysis of RBCs. It affects almost always the second Rh+ve fetus of Rh-ve mother.

Mechanism: when the Rh-ve mother deliver her Rh+ve fetus, some fetal RBCs (which contains D antigen) escapes to the Rh-ve maternal circulation, this will lead to development of anti D antibodies in the plasma of the mother.

This first newborn often will not be affected, but the victim is the second Rh+ve fetus for this mother. This is because the newly developed anti D Ab (IgG) pass through the placenta to destroy the RBCs of this fetus.

Prevention: 1- injecting all the Rh-ve mothers with anti D Ab within 48 hr after delivery. This will destroy the fetal RBCs (D antigens) before they stimulate immune response.

2- Rh-ve female better to avoid marriage with Rh+ve male (so difficult).

3- Never transfuse Rh+ve blood to Rh-ve female.

Treatment: by exchange transfusion to the diseased baby.

Blood transfusion

During blood transfusion, we have to know the blood group of both the donor and the recipient, because if they was incompatible with each other → reaction between the antigen of the donor and the antibody of the recipient → agglutination & Hemolysis.

The donor antibodies do not affect the recipient antigens, because the donor's plasma will be diluted with the recipient plasma.

The O –ve blood group is called universal donor (because has no any antigens).

